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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,268	06/14/2006	Jurgen Kleinschmidt	03528.0149.PCUS00	3309
27194	7590	11/12/2008	EXAMINER	
HOWREY LLP-CA C/O IP DOCKETING DEPARTMENT 2941 FAIRVIEW PARK DRIVE, SUITE 200 FALLS CHURCH, VA 22042-2924			LONG, SCOTT	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/560,268	KLEINSCHMIDT ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 15 September 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 11, 16-18 and 20 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 11, 16-18 and 20 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/16/2008 has been entered.

### ***Claim Status***

Claims 11, 16-18 and 20 are pending. Claims 1-10, 12-15 and 19 are cancelled. Claim 11 is amended. Claims 11, 16-18 and 20 are under current examination.

### ***Priority***

This application claims benefit as a 371 of PCT/EP04/006222 (filed 6/9/2004). The application also claims benefit from foreign application EPO 03013169.2 (filed 6/11/2003). The instant application has been granted the benefit date, 11 June 2003, from the application EPO 03013169.2.

***Sequence Compliance - Drawings***

The examiner had indicated in the Final Action (filed 4/16/2008), that the detailed description of Figure 1 was objected to. In a telephonic interview (7/15/2008), the applicant's representative informed the examiner that an amendment to the Specification (filed 1/30/2008) contained changes which make the objection of 4/16/2008 moot. The examiner thanks the applicant for clarifying this issue. The examiner hereby withdraws the objection to the specification.

***RESPONSE TO ARGUMENTS***

***Claim Rejections 35 USC § 112, second paragraph***

The rejections of Claim 11 under 35 USC 112, second paragraph are withdrawn in response to the applicant's claim amendments and/or arguments.

Applicant's arguments (Remarks, pages 3-4) and Claim amendments, filed 16 July 2008, with respect to claim 11 have been fully considered and are persuasive. The rejections of Claim 11 under 35 USC 112, second paragraph, have been made moot by the claim amendments.

Therefore, the examiner hereby withdraws the rejection of claim 11 under 35 USC 112, second paragraph.

***Claim Rejections 35 USC § 112, first paragraph***

The rejections of claims 11, 16-18 and 20 under 35 USC 112, first paragraph are withdrawn in response to the applicant's claim amendments and/or arguments.

Applicant's arguments (Remarks, pages 4-5) and Claim amendments, filed 16 July 2008, with respect to claims 11, 16-18 and 20 have been fully considered and are persuasive.

The applicant has argued that the claim amendments have narrowed the claimed invention to a method of gene therapy comprising delivery of a specific AAV vector. The applicant further argues that undue experimentation is not necessary to extrapolate from the high reporter gene expression levels demonstrated by the instant examples to using a therapeutic gene. Although, the examiner does not believe the instant specification has not shown a therapeutic use for the specific vector of the instant claims. While the preamble is drawn to a method of gene therapy, in actual method steps are drawn to delivering to a patient an AAV-2 vector. The claimed method steps are enabled in the examiner's view. Therefore, the examiner finds the applicant's arguments persuasive.

Accordingly, the examiner hereby withdraws the rejection of claims 11, 16-18 and 20 under 35 USC 112, first paragraph (lack of enablement).

***Claim Rejections 35 USC § 102***

The rejections of Claims 11, 16-18 and 20 under 35 USC 102(e) as being anticipated by Warrington et al. (US2006/0088936, published 27 April 2006) are withdrawn in response to the applicant's claim amendments and/or arguments.

Applicant's arguments (Remarks, page 6) and Claim amendments, filed 16 July 2008, with respect to claims 11, 16-18 and 20 have been fully considered and are persuasive.

The applicant has amended the claims to require an AAV vector comprising a double mutant R484E and R585E. These specific mutations are not taught by Warrington et al. as a double mutant. Therefore, the reference cannot anticipate the instant claims.

Therefore, the examiner hereby withdraws the rejection of claims 11, 16-18 and 20 under 35 USC 102(e) as being anticipated by Warrington et al.

***Claim Rejections 35 USC § 103***

The rejections of claims 11, 16-18 and 20 rejected under 35 U.S.C. 103(a) as being unpatentable over Bartlett et al. (US Patent 6,962,815, issued 8 November 2005) in view of Kaplitt et al. (US Patent, 6,162,796, issued 19 December 2000) and further in view of Wu Xiao (PhD Dissertation 2002, University of Florida) are withdrawn in response to the applicant's claim amendments and/or arguments.

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Applicant's arguments (Remarks, pages 6-7) and Claim amendments, filed 16 July 2008, with respect to claims 11, 16-18 and 20 have been fully considered and are persuasive.

The applicant has amended the claims to require an AAV vector comprising a double mutant R484E and R585E. These specific mutations are not taught by the cited art as a double mutant. Therefore, there can be no obviousness of the claimed invention based on the cited references.

Therefore, the examiner hereby withdraws the rejection of claims 11, 16-18 and 20 under 35 U.S.C. 103(a) as being unpatentable over Bartlett et al. in view of Kaplitt et al. and further in view of Wu Xiao.

### ***NEW GROUNDS OF REJECTION***

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 16-18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Warrington et al. (US2006/0088936, published 27 April 2006) in view of Bartlett et al. (US Patent 6,962,815, issued 8 November 2005) and further in view of Kaplitt et al. (US Patent, 6,162,796, issued 19 December 2000) and further in view of Wu Xiao (PhD Dissertation 2002, University of Florida).

Claim 11 is directed to a method of gene therapy in a heart muscle tissue of a patient, comprising delivering to a patient an AAV-2 vector or an AAV particle having a capsid encoded by the AAV-2 vector, wherein the AAV-2 vector carries mutations in a heparin-binding motif of a capsid protein and causes a reduced or eliminated heparin binding function, wherein said mutations are R484E/R585E, wherein amino acids R484 and R5895 belong to different capsid protein subunits.



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Warrington et al. teach “recombinant adeno-associated viral (rAAV) vectors having mutations in one or more capsid proteins. Exemplary vectors are provided that have altered affinity for heparin or heparin sulfate” (abstract). Warrington et al. teach rAAV vectors...comprising...R585A ...mutation, affinity for heparin sulfate binding by the vector was eliminated.” (page 3, parag.0028) Warrington et al. disclose rAAV comprising identify mutant R484A as having reduced heparin binding (page 8, parag.0075). Warrington et al. teach delivery of AAV vectors by intravenous administration. . Although, Warrington et al. does not recognize that their vectors will target specifically to cardiac tissue, they do teach that these mutations will alter tropism of the AAV.

While Warrington et al. recognizes the importance of mutations to R484 and R585 for heparin binding of AAV-2 vectors, Warrington does not specifically recommend mutating them to Glutamic Acid (E). Warrington et al. describe a studies of heparin binding based on AAV vectors comprising R484A or R585A. Additionally, Warrington et al. teach double mutants comprising R585A/R588A, suggesting the possibility of double mutant AAV vectors having at least one of the claimed mutations. In addition, Warrington suggests that “conservative double mutant R585K/R588K, and the heparin positive mutant, N587A, was indistinguishable from wild type” in regard to heparin binding motif-related transduction related (page 32, parag.0255). Since both Arginine (R) and Lysine (K) are strongly basic, polar amino acids, a skilled artisan would conclude that substitutions of the important amino acids R585 and R484 with other amino acids besides basic, polar amino acids would be preferable. In further support of

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this line of thinking, Warrington et al. teach “the determinants of HS-protein interactions suggests that their association is driven mainly by electrostatic attraction between acidic sulfate groups on the polysaccharide and basic R-groups on amino acids in the target protein....It was hypothesized that similar electrostatic interactions would govern HSPG-AAV2 association.” (page 29, parag.0242). So, a skilled artisan would understand that altering the amino acids of AAV capsids important for heparin binding function would require changing the from the basic, Arginine, to a neutral or perhaps strongly acidic amino acid, such as Glutamic Acid (E). Furthermore, Warrington et al. suggest that R484 and R585, being involved in the heparin binding motif, “contribute to a basic patch on one side of each three-fold related spike” (page 33, parag. 0265), indicating how vulnerable this motif would be to disruption by substitution of an alternative acidic amino acid (such as glutamic acid (E) for the critical basic amino acids (arginines) of R484 and R585.

In addition, Warrington et al. suggest the nexus between R484 and R585, “R484, which is basic in all five serotypes was tested because of its proximity to R585 and R588, and subsequently proved to be involved in heparin binding” (page 33, parag.0261). As indicated above, Warrington et al. suggest the idea of using double mutant AAV vectors. Warrington et al. also indicated that “[m]utants that contained substitutions at both positions had even lower infectivity” (page 33, parag.0262), demonstrating the double mutants could be advantageous over single mutations. Warrington et al. suggest that amino acids R484 and R585 belong to different capsid protein subunits, when discussing the position of these amino acids in relation to the

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atomic structure of AAV2, "residues R585 and R588, which are contributed by one of the peptides in the trimer, are positioned above a linear arrangement of R484, R487, and K532, which are contributed by a second peptide in the trimer. Thus it appears that a heparin binding motif is formed from some combination of these five amino acids using amino acids from two different polypeptides" (page 33, parag. 0265).

Bartlett et al. teach, "Recent research on AAV has therefore involved attempts to modify the viral genome. As the range of cells that AAV will infect is so broad, some researchers have focused on modifying the virus so that it targets specific types of cells for infection. The cellular range or tropism of the virus is determined by the binding of AAV capsid protein(s) to receptor and/or coreceptor proteins expressed on the surface of target cells. Heparin-sulfate proteoglycans (HSPG) is the primary cellular attachment receptor for AAV2." (col.2, lines 11-19). Bartlett et al. further teach, "AAV vectors of the invention that exhibit an altered cellular tropism may differ from wild type in that the natural tropism of AAV may be reduced or abolished" (col.4, lines 41-65). The instant application states, "Mutational analysis of AAV-2 capsid proteins VP1, VP2 and VP3, respectively showed that a group of basic amino acids (arginines 484, 487, 585, 588 and lysine 532; numbering according to the numbering based on VP1 protein id AAC03780.1 NCBI accession No. AF043303) contributes to heparin and HeLa cell binding. These amino acids are positioned in three clusters on the threefold spikes of the AAV-2 capsid." (page 4, 1<sup>st</sup> parag.). Bartlett et al. further teach amino acids 584 and 588 of VP1 as being important to heparin binding (col.17, lines 1-7 and col.41, line 26). This AAV vector contains at least one mutation to the capsid proteins in amino acid

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positions 470 to 592, which affects heparin binding. Bartlett et al. teach "The AAV-RGD vectors A588-RGD4C-eGFP and A588-RGD4CGLS were tested for their ability to target gene transfer to the ovarian cell lines as described in Example 9...were able to more efficiently direct gene transfer...compared to wild type AAV vector containing unmodified capsid" (col.19, lines 56-64).

Bartlett et al. do not teach specific delivery of AAV to heart muscle tissue and do not explicitly teach AAV mutants comprising amino acid substitutions R484E and R585E. However, Bartlett et al. do teach the general concept of AAV-2 vectors comprising double mutations of amino acids important for heparin binding.

Kaplitt et al. teach, "AAV naturally infects heart muscle...AAV vectors can yield long-term expression not observed with other systems" (parag.0025) and "the present invention results in gene transfer and expression to a wide area of heart muscle" (parag.0027).

Kaplitt et al. do not teach the specific mutations of capsid proteins and its corresponding effect on heparin-sulfate binding proteins as required by the instant claims.

However, Wu Xiao et al. teach "to increase the targeting of rAAV vectors...1) reducing the natural tropism of AAV, and 2) increasing the tissue specificity of AAV...[have been attempted by] groups [of researchers who] have been trying to locate sites of AAV capsid for receptor binding and the sites exposed on the surface of the capsid by doing extensive capsid mutagenesis experiments" (page 14, lines 6-10). Wu

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Xiao also teaches “double mutants at amino acid 585 and 588 of AAV capsid protein abolish its heparin binding activity” (page 14, lines 19-20).

Claims 16-18 are directed to further limitations of the claims, wherein the AAV capsid proteins are VP1 (claim 17); VP1, VP2, or VP3 (claim 16); number of amino acid position is according to VP1 (claim 18). Claim 20 is directed to system delivery of the AAV. All of the limitations of claims 16-18 and 20 are taught by the cited references.

It would have been obvious to one skilled in the art to use an AAV vector having mutations to the capsid proteins in amino acid positions 484 and 585, which affects heparin binding in a method of gene therapy to heart muscle tissue.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (mutations to AAV-2 capsid protein at positions 484 and 585; and AAV having a specificity for heart muscle tissue) are taught by Warrington, Bartlett, Kaplitt, and Wu Xiao. Wu Xiao, in particular, teaches that mutations of capsid proteins are capable of limiting the range of cellular targeting by AAV.

In addition, the claimed invention is obvious because “a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and commonsense.” The prior art teaches the need in the art to solve the problem

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of optimally "disrupting the heparin binding site on AAV-2 vectors used for gene delivery" and further identifies a number of predictable potential solutions for making mutations to the heparin binding motif of AAV-2, including mutating both amino acid positions R484 and R585. The possible number of alternative amino acids is limited and furthermore, the prior art clearly recommends against a strongly basic amino acid as the substitution for Arginine. All of the potential solutions would have been known by a skilled artisan. One of ordinary skill in the art could have pursued the known potential options (of substituting non-basic amino acids for the arginines of R484 and R585) with a reasonable expectation of success. Therefore, it would be predictably obvious to use alternative amino acids when creating the R484E/R585E AAV-2 double mutant.

Therefore the methods as taught by Warrington et al., in view of Bartlett et al. and further in view of Kaplitt et al. and further in view of Wu Xiao would have been *prima facie* obvious over the method of the instant application.

### ***Conclusion***

No claims are allowed.

***Examiner Contact Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long  
Patent Examiner, Art Unit 1633  
/Janet L. Epps-Ford/  
Primary Examiner, Art Unit 1633